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AI-POWERED PHARMACOKINETICS: A COMPREHENSIVE REVIEW OF COMPUTATIONAL METHODS FOR ADME PREDICTION

Sahana V. M. Vats[1]* and Sunil Kumar[2]

[1]Associate Professor, Dept. of Dravya Guna, National College of Ayurveda & Hospital, Barwala, Hisar.

[2]Associate Professor, Dept. of Agad Tantra, BDM College of Ayurveda Science & Hospital, Chhuchhakwas, Jhajjar.

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***Corresponding Author**
Dr. Sahana V. M. Vats
Associate Professor, Dept. of Dravya Guna, National College of Ayurveda & Hospital, Barwala, Hisar.

ABSTRACT

Pharmacokinetics, the study of drug absorption, distribution, metabolism, and excretion (ADME), is pivotal in shaping the efficacy and safety of therapeutic agents. Traditionally driven by in vitro and in vivo experimentation, pharmacokinetic analysis is often resource-intensive, ethically challenging, and limited by species variability. The emergence of artificial intelligence (AI) and machine learning (ML) has ushered in a transformative era, offering predictive models that harness vast datasets to enhance accuracy, speed, and cost-efficiency. This review explores the current landscape of AI-driven computational methods for ADME prediction. It moves into a spectrum of approaches, from Random Forests and Support Vector Machines to Deep Learning and Graph Neural Networks, highlighting their application in predicting absorption rates, volume of distribution, metabolic sites, and excretory pathways. We also examine challenges such as data quality, model interpretability, and regulatory hurdles, and envision a future where AI synergizes with real-world patient data for personalized pharmacokinetics. This confluence of pharmacological tradition and digital innovation heralds a paradigm shift in drug development and individualized therapy.

KEYWORDS: Pharmacokinetics, Artificial Intelligence, Machine Learning, Deep Learning, ADME Prediction, Drug Absorption, Volume of Distribution, Plasma Protein Binding,

Blood-Brain Barrier Permeability, Metabolic Stability, Cytochrome P450, Drug Metabolism, Drug Excretion, Renal Clearance, Biliary Excretion, Support Vector Machines, Random Forest, Neural Networks, Graph Neural Networks, QSAR, Physiologically Based Pharmacokinetic Modeling, Transporter Proteins, P-glycoprotein, Molecular Descriptors, Drug-Drug Interactions, Virtual Screening, Personalized Medicine, Explainable AI, AI in Drug Discovery, Computational Pharmacology.

INTRODUCTION

Pharmacokinetics (PK), the study of a drug's absorption, distribution, metabolism, and excretion (ADME), is fundamental to drug development, influencing both efficacy and safety profiles. Traditionally, determining these parameters has relied on in vitro and in vivo experiments, which are time-consuming, resource-intensive, and often involve ethical concerns related to animal testing.[1] Moreover, these conventional methods may not always accurately predict human responses due to interspecies differences.

The advent of artificial intelligence (AI) and machine learning (ML) has introduced transformative tools in pharmacokinetics. These computational approaches can analyze vast datasets to predict ADME properties, thereby reducing the reliance on extensive laboratory experiments. AI-driven models have shown promise in enhancing the accuracy and efficiency of pharmacokinetic predictions, facilitating faster and more cost-effective drug development processes.[2]

Recent studies have demonstrated the application of various AI algorithms, such as Random Forests, Artificial Neural Networks, and Deep Neural Networks, in predicting pharmacokinetic parameters like clearance and volume of distribution.[3] These models have been trained on large datasets, enabling them to identify complex patterns and relationships that traditional statistical methods might overlook.

Furthermore, integrating AI with physiologically based pharmacokinetic (PBPK) modeling has shown potential in simulating drug concentration-time profiles, offering a more comprehensive understanding of drug behaviour in the human body.[4] This integration allows for the prediction of pharmacokinetic parameters in various populations, including those with specific physiological or pathological conditions.

Despite these advancements, challenges remain in the widespread adoption of AI in pharmacokinetics. Issues such as data quality, model interpretability, and regulatory acceptance need to be addressed to fully realize the potential of AI-driven pharmacokinetic modeling.

This review aims to provide a comprehensive overview of the current computational methods employing AI for ADME prediction. We will explore various AI techniques, including deep learning and neural networks, and their applications in modeling drug absorption, distribution, metabolism, and excretion. Additionally, we will discuss the challenges and future prospects of integrating AI into pharmacokinetic studies, highlighting its potential to revolutionize the field of drug development.

AI in Absorption Prediction

Absorption is the very first gatekeeper in the journey of any drug molecule, determining whether it even makes it into the bloodstream to perform its magic. This phase directly controls the drug's bioavailability, the proportion of the administered dose that reaches systemic circulation intact, and it largely dictates the onset and intensity of the drug's therapeutic effect. At the core, absorption involves the drug crossing complex biological membranes, primarily the epithelial lining of the small intestine, via passive diffusion, facilitated transport, or active transport mechanisms.[5]

Traditional challenges in absorption prediction

Historically, absorption has been assessed through in vitro cell-based models such as Caco-2 cell monolayers, which mimic intestinal epithelium permeability, and in vivo animal studies, primarily rodent models. While these methods provide valuable experimental insights, they come with significant limitations such as

Ethical concerns- Animal testing raises ethical dilemmas and regulatory hurdles, which have grown increasingly stringent.

Cost and time- In vitro and in vivo tests are time-consuming and expensive, slowing early drug development.

Scalability issues- These methods cannot efficiently screen thousands of molecules in large compound libraries.

Species differences- Animal models don't always translate to human physiology due to interspecies variability, leading to inaccurate predictions of human absorption.

The AI Revolution in Absorption Prediction

Enter artificial intelligence, especially machine learning (ML), a game-changer that harnesses vast chemical data to predict absorption without physical experiments. ML models rely on molecular descriptors, quantitative numerical representations of molecular properties, which correlate with absorption tendencies. These descriptors encompass as

Physicochemical properties- Molecular weight, lipophilicity (logP), aqueous solubility.

Structural features- Number of hydrogen bond donors and acceptors, topological polar surface area (TPSA).

Electronic characteristics- Partial charges, polarizability.

Among ML algorithms, Random Forest (RF) and Support Vector Machine (SVM) have proven highly effective due to their ability to model complex nonlinear relationships between descriptors and absorption outcomes[6]. Wang's team demonstrated that RF and Light Gradient Boosting Machine (LightGBM) models could predict human intestinal absorption with over 85% accuracy on large, diverse datasets—a striking improvement over traditional QSAR methods.

Specialized models for natural products

Interestingly, for natural product drug discovery, an area increasingly valued for novel therapeutics, simpler algorithms sometimes shine. For example, Decision Tree (DT) models can effectively classify absorption behavior when the chemical space is narrower or structurally related, such as phytomolecules from medicinal plants. Study showed a DT model achieving an impressive 98% accuracy in predicting intestinal absorption of compounds from Cichorium intybus, outperforming more complex algorithms like RF and SVM.[7] This finding suggests that when the dataset is chemically homogeneous, the interpretability and simplicity of DT models offer advantages, allowing researchers to glean mechanistic insights rather than "black box" predictions.

Advanced AI Techniques: Graph neural networks

Pushing the frontier further, Graph Neural Networks (GNNs) have revolutionized molecular property prediction. Unlike traditional descriptors, GNNs treat molecules as graphs, where atoms are nodes and bonds are edges, preserving the spatial and relational information of molecular structures. This method allows the AI to learn directly from raw molecular structures, capturing subtle patterns that influence absorption but are missed by fixed descriptors.[8]

GNNs have been integrated into platforms like admetSAR 2.0 and ADMETlab 2.0, which combine multiple AI algorithms—including RF, SVM, and GNNs—to provide holistic ADMET property predictions, including absorption, with enhanced accuracy and usability for researchers worldwide.[9]

Mechanistic Insights and Drug Screening Benefits

AI doesn't just predict absorption; it helps scientists understand why certain molecules absorb well or poorly. By analyzing feature importance in ML models, researchers identify critical molecular traits that promote membrane permeability or trigger efflux by transport proteins like P-glycoprotein. This insight drives rational drug design, optimizing lead compounds before synthesis or costly testing.

Moreover, AI accelerates high-throughput virtual screening, filtering vast compound libraries to flag molecules with poor predicted bioavailability early, saving precious time and resources in drug discovery pipelines.[10]

AI in Distribution Prediction

Once a drug successfully crosses the absorption barrier, its fate within the body is shaped by distribution, the process dictating how the compound disperses across various tissues, organs, and body fluids. Distribution profoundly impacts the therapeutic efficacy of the drug by determining whether sufficient concentrations reach the target site, while also influencing toxicity by governing accumulation in non-target tissues.[11]

Core Parameters of Distribution

The main pharmacokinetic parameters defining distribution include

Volume of Distribution (Vd): Reflects the extent to which a drug partitions between plasma and tissues; a large Vd implies extensive tissue binding or sequestration.

Plasma Protein Binding: Only unbound (free) drug molecules can diffuse into tissues; hence, binding to albumin or alpha-1-acid glycoprotein influences distribution.

Tissue Permeability: The ability of drugs to cross biological barriers such as the blood-brain barrier (BBB) or placental barrier.

These parameters depend largely on molecular characteristics such as lipophilicity, molecular size, charge, and affinity for transport proteins.[12]

Traditional Approaches- Pros and Cons

Historically, distribution studies relied on in vivo animal experiments and radiolabeled drug tracing, which provide direct but often resource-intensive and ethically fraught data. Moreover, species-specific physiological differences complicate extrapolation to humans, undermining translational accuracy.[13]

AI-Driven Models Transforming Distribution Prediction

The advent of AI has revolutionized this landscape, offering scalable, cost-effective, and increasingly accurate computational methods.

Random Forest (RF) and Support Vector Regression (SVR) have become workhorses in predicting Volume of Distribution (Vd). Random Forest (RF) is like a big group of decision trees (tiny yes/no questions about a molecule) working together to make a better prediction. Think of it as a forest of trees "voting" on what they think will happen.[14] Support Vector Regression (SVR) is another kind of algorithm that tries to draw the best line (or curve) through data points to predict outcomes—kind of like a super-precise guesser. Study shows[15] trained RF models on diverse drug libraries, achieving robust correlations ($R^2 > 0.7$) between predicted and experimental Vd values, indicating the models' ability to capture complex nonlinear relationships rooted in molecular descriptors.

Artificial Neural Networks (ANNs) go a step further by modeling intricate nonlinearities in pharmacokinetic behaviors. ANN models surpass conventional ML in predicting tissue-specific distribution, notably in forecasting BBB permeability, a notoriously difficult barrier to model due to its selective transport mechanisms.[16]

Incorporating biological factors for enhanced prediction

AI models that integrate biological data, such as plasma protein binding affinity, achieve superior predictions by estimating the biologically active free drug fraction. Zhou et al. (2020) combined plasma protein binding parameters with ML algorithms to refine estimates of free drug concentrations in plasma and tissues, improving accuracy in predicting pharmacologically relevant distribution.

Moreover, ligand-protein docking simulations and molecular dynamics (MD) powered by AI illuminate drug interactions with key transporters and efflux pumps such as P-glycoprotein (P-gp). These transporters regulate drug passage into sensitive tissues like the brain, affecting

both efficacy and toxicity. AI-driven docking studies to predict transporter binding affinities, offering mechanistic insights into tissue-specific drug accumulation.[17]

Accessible AI Platforms for Distribution Prediction

Several user-friendly platforms embody these AI advances, democratizing access to complex distribution predictions:

pkCSM employs graph-based molecular signatures alongside ML to forecast multiple pharmacokinetic properties, including Vd and BBB permeability.[18] Its interpretability and accuracy have made it a popular tool in drug discovery pipelines.

SwissADME, a widely used academic and industrial tool, incorporates AI-augmented algorithms to predict ADME features, particularly distribution parameters, integrating chemical properties with machine learning models for broad applicability.[19]

Impact on drug development

AI-enhanced distribution models reduce late-stage clinical failures by predicting risks of drug accumulation and toxicity early in development. They also guide dosing strategies, helping maintain effective drug concentrations in target tissues while minimizing off-target effects, a delicate balance critical for personalized medicine.[20]

AI in Metabolism Prediction

Metabolism is the biochemical transformation of drugs, primarily occurring in the liver, orchestrated by enzymatic players, chief among them, the cytochrome P450 (CYP450) enzyme family. This metabolic processing governs a drug's half-life, therapeutic efficacy, and potential for toxic side effects. Predicting how a molecule will be metabolized is crucial early in drug development to weed out compounds prone to rapid clearance or harmful metabolites.[21]

Traditional metabolism studies: The bottleneck

Conventionally, metabolism studies rely on in vitro incubations with human liver microsomes, hepatocytes, or recombinant enzymes, followed by complex analysis with mass spectrometry to identify metabolites and quantify metabolic rates. These experimental approaches, while gold standards, are time-consuming, expensive, and limited in throughput. They also often fail to fully predict in vivo metabolic profiles due to the liver's complex environment and extrahepatic metabolism.[22]

Enter AI Predicting Metabolism with Data and Patterns

Artificial intelligence, leveraging vast chemical and biological datasets, has ushered in a new era of metabolism prediction. By decoding molecular features and enzyme interaction patterns, AI models predict both sites of metabolism (SOM), specific atoms or bonds within molecules prone to enzymatic attack—and metabolic stability, enabling early-stage screening.

Random Forest (RF) and Support Vector Machine (SVM) models have been frontline tools. In a study an RF-based model trained on known CYP450 substrates that predicted metabolic susceptibility with high specificity constructed.[23] Their model enabled rapid identification and elimination of drug candidates likely to undergo extensive metabolism, saving precious development time.

Deep Learning, especially Convolutional Neural Networks (CNNs), has supercharged the prediction of metabolic sites. Ryu et al. (2018) employed CNNs to analyze molecular graphs, capturing subtle structural motifs and electronic environments that govern CYP450 binding and catalytic action.[24] This approach achieved superior accuracy over classical ML by effectively learning the spatial and chemical context of potential metabolic hotspots.

Beyond SOM- Predicting Metabolic Pathways and Drug-Drug Interactions

AI models are not limited to pinpointing metabolic sites. They also forecast the types of metabolites formed and predict drug-drug interactions (DDIs) mediated by metabolism, critical for polypharmacy safety.

A study highlighted how integrating biochemical pathway knowledge with AI models aids in understanding how multiple drugs might compete for or inhibit CYP450 enzymes, thus modulating metabolism rates and potentially causing adverse effects.[25]

This systems-level AI approach incorporates enzyme kinetics, genetic polymorphisms, and co-administered drug profiles, providing a holistic prediction platform for metabolism-related drug interactions.

AI-Powered Tools for Metabolism Prediction

Several publicly accessible tools embody these advances

MetaPred uses machine learning to predict SOMs and provides metabolite structure predictions, enabling medicinal chemists to anticipate metabolic liabilities.[26]

FAME 3 (Fast Metabolizer) integrates graph-based algorithms and ML to predict both phase I and phase II metabolic transformations, offering insights into metabolic stability and pathways.[27]

These platforms enable high-throughput virtual screening of metabolism, reducing reliance on laborious lab work and accelerating the lead optimization cycle.

The road ahead

AI in metabolism prediction is rapidly evolving. Future models are expected to integrate multi-omics data, such as transcriptomics and proteomics of liver tissues, with chemical structure information to capture dynamic, personalized metabolism profiles.[28] This will support precision pharmacokinetics, tailoring drug dosing to individual metabolic capacities.

By accurately forecasting metabolic transformations and interactions, AI not only streamlines drug discovery but also enhances patient safety, a quintessential leap toward smarter, faster, and safer therapeutics.

AI in Excretion Prediction

Excretion represents the grand finale in the pharmacokinetic saga, the body's way of clearing out drugs and their metabolites through renal, biliary, and sometimes pulmonary pathways. The efficiency of excretion dictates drug clearance, influences half-life, and ultimately impacts safety profiles. Yet, predicting excretion is no walk in the park. Biological complexity, involvement of multiple organs, transporter proteins, and overlapping mechanisms pose a huge challenge for traditional experimental assays, which are often time-consuming, costly, and incomplete.[29]

Enter AI, the computational game-changer. Leveraging vast ADMET datasets and molecular descriptors, AI models excel in decoding the convoluted determinants of excretion. For instance, Random Forest (RF) and Gradient Boosting Machine (GBM) algorithms trained on human renal clearance data have demonstrated promising predictive accuracy. These models use features like molecular weight, polarity, topological polar surface area, and affinity for excretory transporters to estimate renal clearance rates with considerable reliability.

Transporter proteins, such as organic anion transporters (OATs), organic cation transporters (OCTs), and P-glycoprotein, act as biological gatekeepers for excretion, mediating drug efflux into urine or bile. AI has harnessed molecular docking coupled with machine learning classification techniques to predict substrate affinity for these transporters, a crucial step in anticipating excretion profiles. AI-enhanced docking and ML classifiers to predict interactions with P-glycoprotein, revealing key structural motifs responsible for transporter-mediated excretion.[30] This integrated approach not only enhances mechanistic understanding but also flags molecules at risk for altered clearance due to transporter inhibition or induction.

Publicly accessible platforms like admet SAR 2.0, which incorporate multiple AI algorithms including RF and support vector machines, provide user-friendly excretion prediction modules. These tools facilitate early-stage drug screening by flagging candidates with unfavorable excretion profiles, ultimately preventing accumulation-related toxicity.[31]

Accurate AI-driven excretion predictions thus serve as vital guardrails in drug development pipelines. By forecasting clearance patterns, these models help optimize dosing regimens, minimize adverse effects stemming from drug accumulation, and safeguard patient well-being. In the era of precision medicine, marrying AI with pharmacokinetics for excretion prediction is not just an innovation, it's a necessity.

Challenges and Future perspectives

Despite the meteoric rise of AI in predicting pharmacokinetic parameters, several stubborn challenges still cast long shadows over its widespread adoption. The first and perhaps most glaring hurdle is data quality and availability. AI models are data-hungry beasts, they thrive on large, diverse, and meticulously curated datasets to learn meaningful patterns. Unfortunately, pharmacokinetic data are often fragmented, inconsistent, or derived from heterogeneous experimental setups that vary across labs and species. This patchwork of information introduces noise and biases, which compromise model reliability and generalizability. Although initiatives aimed at standardizing experimental protocols and creating centralized, open-access repositories are underway, progress is slow and fraught with logistical complexities.[32]

Beyond raw data, the interpretability of AI models presents another formidable challenge. Sophisticated models like deep neural networks often operate as inscrutable "black boxes," delivering predictions without transparent reasoning. For clinical and regulatory stakeholders,

this opacity breeds mistrust and hinders adoption, especially when patient safety is on the line. The push for explainable AI (XAI) is gaining momentum, aiming to peel back layers of complexity to reveal the "why" and "how" behind predictions. Methods such as SHAP (SHapley Additive exPlanations) and LIME (Local Interpretable Model-agnostic Explanations) offer glimpses into feature importance and decision logic, but the field remains in flux, with no silver bullet yet.[33]

Regulatory acceptance adds another layer of complexity. For AI-driven pharmacokinetic models to become a staple in drug development and clinical practice, agencies like the FDA and EMA require rigorous validation, reproducibility, and evidence of clinical utility across diverse populations and contexts. The evolving regulatory landscape is cautiously optimistic but demands transparency, risk assessment, and integration with existing frameworks (FDA, 2023).[34]

Looking ahead, the fusion of AI with electronic health records (EHRs) and real-world patient data holds the promise of truly personalized pharmacokinetics. Models could incorporate genetic, demographic, and lifestyle factors to predict drug absorption, metabolism, and clearance at the individual level, a leap beyond the one-size-fits-all paradigm. Achieving this vision necessitates seamless collaboration between academia, industry, and regulators to foster data sharing, harmonize standards, and co-develop robust validation pipelines.[35]

In essence, while AI's promise in pharmacokinetics is tantalizing, it requires overcoming significant technical, ethical, and infrastructural barriers. The journey demands a measured balance of innovation and caution, transparency and complexity, competition and collaboration, a symphony of efforts to rewrite the future of drug development and patient care.

CONCLUSION

The integration of AI into pharmacokinetics is no mere incremental step; it's a paradigm shift that redefines how we understand and predict the fate of drugs within the human body. From absorption to excretion, AI models, fueled by vast molecular data and advanced algorithms, offer unprecedented precision in forecasting ADME profiles. This leap forward promises to streamline drug development, reduce costly late-stage failures, and minimize ethical concerns tied to animal testing. The ability to predict complex phenomena such as metabolic stability, tissue distribution, and renal clearance with machine learning and deep learning not only

accelerates the pace of innovation but also enhances the safety profile of candidate drugs before they ever reach clinical trials.

Yet, this journey is far from seamless. The reliance on large, high-quality datasets exposes a glaring vulnerability: data scarcity and inconsistency can cripple AI performance, limiting its generalizability. Moreover, the "black box" nature of many AI models poses a challenge for scientific transparency and regulatory acceptance. Without clear explanations of how predictions are made, clinicians and regulators may hesitate to fully trust these tools. This highlights the urgent need for explainable AI, models that don't just predict but justify their outputs in biologically meaningful ways.

Looking to the horizon, the true power of AI in pharmacokinetics will unfold through integration, with electronic health records, patient-specific genetic data, and real-world clinical outcomes, ushering in the era of personalized medicine. Imagine drug regimens tailored not only to a molecule's chemistry but also to an individual's unique biology, lifestyle, and environment. Such precision is the holy grail, and AI is the torchbearer lighting the way.

Achieving this vision demands collaboration across disciplines, pharmacologists, data scientists, clinicians, and regulatory bodies must unite to standardize data, validate models robustly, and ensure ethical implementation. Only then can AI transcend from a promising tool to an indispensable pillar of modern drug discovery and therapeutic optimization.

In essence, AI-powered pharmacokinetics embodies a fusion of time-honored pharmacological principles with cutting-edge computational innovation. It beckons us to embrace the future without forsaking the rigor of the past—a delicate balance that will ultimately shape safer, more effective, and deeply personalized therapies for generations to come.

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